Vaxcel®

METHYLPREDNISOLONE 500mg

FOR INJECTION OR INFUSION

MAL25106005AZ

COMPOSITION:
Each vial contains: Methylprednisolone (as methylprednisolone sodium succinate) 500mg

PRESENTATION:
A white or almost white, hygroscopic powder. The reconstituted solution should be clear colourless to clear light yellowish solution.

INDICATIONS:
Glucocorticoids should only be considered as a purely symptomatic treatment, unless in case of some endocrine disorders, where they are used as substitution treatment.

Anti-Inflammatory Treatment :
Rheumatic Disorders (as adjunctive therapy for short-term administration in the management of an acute episode or exacerbation) :
- Post-traumatic osteoarthritis
- Synovitis of osteoarthritis
- Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy)
- Acute and subacute bursitis
- Epicondylitis
- Acute non-specific tenosynovitis
- Acute gouty arthritis
- Psoriatic arthritis
- Ankylosing spondylitis

Collagen Diseases (during an exacerbation or as maintenance therapy in selected cases of) :
- Systemic lupus erythematosus
- Acute rheumatic carditis
- Polyarteritis nodosa
- Good pasture's syndrome
- Systemic dermatomyositis (polymyositis)

Dermatologic Diseases :
- Pemphigus
- Severe erythema multiforme (Stevens-Johnson syndrome)
- Exfoliative dermatitis
- Bullous dermatitis herpetiformis
- Severe seborrheic dermatitis
- Severe psoriasis
- Mycosis fungoides
- Urticaria.

Allergic States (to control severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in) :
- Bronchial asthma
- Contact dermatitis
- Atopic dermatitis
- Serum sickness
- Drug hypersensitivity reactions
- Urticarial transfusion reactions
- Acute non-infectious laryngeal oedema (epinephrine is the drug of first choice)

Ophthalmic Diseases (severe acute and chronic allergic and inflammatory processes involving the eye) :
- Herpes zoster ophthalmicus
- Iritis, iridocyclitis
- Chorioretinitis
- Diffuse posterior uveitis and choroiditis
- Optic neuritis
- Sympathetic ophthalmia

Gastrointestinal Diseases (to manage critical period of the disease in) :
- Ulcerative colitis (systemic therapy)
- Crohn's disease (systemic therapy).

Respiratory Diseases :
- Symptomatic pulmonary sarcoidosis
- Berylliosis
- Aspiration pneumonitis.
- Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate anti-tuberculous chemotherapy
- Loeffler's Syndrome not manageable by other means

Edematous States :
- To induce diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.

Immunosuppressive Treatment :
Organ transplantation.

Treatment of Hematological and Oncological Disorders :
Hematologic Disorders :
- Acquired (autoimmune) haemolytic anemia
- Erythroblastopenia (RBC anemia)
- Congenital (erythroid) hypoplastic anemia
- Idiopathic thrombocytopaenia purpura in adults (IV only; IM administration is contraindicated)
- Secondary thrombocytopenia in adults

Oncological Diseases (for palliative management of) :
- Leukemias and lymphomas in adults
- Acute leukemia of childhood.

Treatment of Shock States :
Shock secondary to adrenocortical insufficiency or shock unresponsive to conventional therapy when adrenal cortical insufficiency may be present. (Hydrocortisone is generally the drug of choice. When mineralocorticoid activity is undesirable, methylprednisolone may be preferred.) Hemorrhagic, traumatic and surgical shock unresponsive to standard therapy. Although there are no well controlled (double-blind placebo) clinical trials, data from experimental animal models indicate that methylprednisolone sodium succinate may be useful in shock states in which standard therapy e.g. fluid replacement has not been effective.

Others :
Nervous System :
- Cerebral oedema from tumour - primary of metastatic and / or associated with surgical or radiation therapy or head trauma
- Acute exacerbations of multiple sclerosis
- Acute spinal cord injury - the treatment should begin within eight hours of injury
- Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculosis chemotherapy
- Trichinosis with neurologic or myocardial involvement
- Prevention of nausea and vomiting associated with cancer chemotherapy

Endocrine Disorders :
- Primary or secondary adrenocortical insufficiency
- Acute adrecocortical insufficiency
- For these indications, the drugs of choice are hydrocortisone or cortisone. Synthetic analogues can be used in certain circumstances if they are combined with mineralocorticoids
- Preoperatively and in the event of serious, trauma or illness, in patients with known adrenal insufficiency or when adrenocortical reserve is doubtful
- Congenital adrenal hyperplasia
- Nonsuppurative thyroiditis
- Hypercalcaemia associated with cancer

PHARMACOLOGY:
Pharmacodynamic Properties:
Methylprednisolone is a potent anti-inflammatory steroid. It has greater anti-inflammatory potency than prednisolone and less tendency than prednisolone to induce sodium and water retention. Methylprednisolone sodium succinate has the same metabolic and anti-inflammatory actions as methylprednisolone. When given parenterally and in equimolar quantities, the two compounds are equivalent in biologic activity. The relative potency of methylprednisolone sodium succinate and hydrocortisone sodium succinate, as indicated by depression of eosinophil count, following intravenous administration, is at least four to one. This is in good agreement with the relative oral potency of methylprednisolone and hydrocortisone.
Methylprednisolone sodium succinate has been investigated for acute spinal cord injury in two randomized, double-blind, comparative National Acute Spinal Cord Injury Studies (NASCIS 2 and 3). The effect of high dose methylprednisolone sodium succinate given as initial bolus of 30 mg/kg by IV for 15 minutes followed 45 minutes later by a continuous infusion of 5.4 mg/kg/hour for 24 hours was significant on neurologic recovery when given to patients within 8 hours from injury (NASCIS 2) and motor recovery was higher for those patients initiated within 3 to 8 hours from injury and treated with the same regimen for 48 hours (NASCIS 3).

Pharmacokinetic Properties:
Methylprednisolone pharmacokinetics is linear, independent of route of administration.

Absorption:
After a 40mg intramuscular dose of methylprednisolone sodium succinate to fourteen healthy adult male volunteers, the average peak concentration of 454ng/mL was achieved at 1 hour. At 12 hours, the methylprednisolone plasma concentration has declined to 31.9ng/mL. No methylprednisolone was detected 18 hours after dosing. Based on area-under-the-time-concentration curve, an indication of total drug absorbed, intramuscular methylprednisolone sodium succinate was found to be equivalent to the same dose administered intravenously. Results of a study demonstrated that the sodium succinate ester of methylprednisolone is rapidly and extensively converted to the active methylprednisolone moiety after all routes of administration. Extent of absorption of free methylprednisolone following IV and IM administrations were found to be equivalent and significantly greater than those following administration of the oral solution and oral methylprednisolone tablets. Since the extent of methylprednisolone absorbed following the IV and IM treatment was equivalent in spite of the greater amount of the hemisuccinate ester reaching the general circulation after IV administration, it appears that the ester is converted in the tissue after IM injection with subsequent absorption as free methylprednisolone.

Distribution:
Methylprednisolone is widely distributed into the tissues, crosses the blood-brain barrier, and is secreted in breast milk. Its apparent volume of distribution is approximately 1.4L/kg. The plasma protein binding of methylprednisolone in humans is approximately 77%.

Metabolism:
In humans, methylprednisolone is metabolized in the liver to inactive metabolites; the major ones are 20α-hydroxymethylprednisolone and 20 β-hydroxymethylprednisolone. Metabolism in the liver occurs primarily via the CYP3A4. Methylprednisolone, like many CYP3A4 substrates, may also be a substrate for the ATP-binding cassette (ABC) transport protein p-glycoprotein, influencing tissue distribution and interactions with other medicines.

Elimination:
The mean elimination half-life for total methylprednisolone is in the range of 1.8 to 5.2 hours. Total clearance is approximately 5 to 6mL/min/kg. No dosing adjustments are necessary in renal failure. Methylprednisolone is hemodialyzable.

DOSAGE AND ADMINISTRATION:
Methylprednisolone sodium succinate may be administered by intravenous (IV) injection or infusion, or by intramuscular (IM) injection. The preferred method for initial emergency use is IV injection. Dosage may be reduced for infants and children but should be selected based on the severity of the condition and the response of the patient rather than on the age or weight of the patient. The pediatric dosage should not be less than 0.5mg/kg every 24 hours.
Dosage requirements are variable and must be individualized on the basis of the disease under treatment, its severity and the response of the patient over the entire duration of treatment. A risk/benefit decision must be made in each individual case on an ongoing basis. The lowest possible dose of corticosteroid should be used to control the condition under treatment for the minimum period. The proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage, which will maintain an adequate clinical response, is reached.
If after long-term therapy the drug is to be stopped, it needs to be withdrawn gradually rather than abruptly. Following the initial emergency period, consideration should be given to employing a longer acting injectable preparation or an oral preparation.

Recommended dosages for methylprednisolone sodium succinate

Indication	Dosage
Adjunctive therapy in life threatening conditions	Administer 30mg / kg IV over a period of at least 30 minutes. Dose may be repeated every 4 to 6 hours for up to 48 hours.
Rheumatic disorders unresponsive to standard therapy (or during exacerbation episodes)	Administer either regimen as IV pulse dosing over at least 30 minutes. The regimen may be repeated if improvement has not occurred within a week after therapy, or as the patient's condition dictates. 1g / day for 1 to 4 days, or 1g / month for 6 months.
Systemic lupus erythematosus unresponsive to standard therapy (or during exacerbation episodes)	Administer 1g / day for 3 days as IV pulse dosing over at least 30 minutes. The regimen may be repeated if improvement has not occurred within a week after therapy, or as the patient's condition dictates.
Multiple sclerosis unresponsive to standard therapy (or during exacerbation episodes)	Administer 500mg / day or 1g / day for 3 or 5 days as IV pulse dosing over at least 30 minutes. The regimen may be repeated if improvement has not occurred within a week after therapy, or as the patient's condition dictates.
Edematous states, such as glomerulonephritis or lupus nephritis, unresponsive to standard therapy (or during exacerbation episodes)	Administer either regimen as IV pulse dosing over at least 30 minutes. The regimen may be repeated if improvement has not occurred within a week after therapy, or as the patient's condition dictates. 30mg / kg every other day for 4 days, or 1 g / day for 3, 5 or 7 days.
Prevention of nausea and vomiting associated with cancer chemotherapy	**For mild to moderately emetogenic chemotherapy :** Administer 250mg IV over at least 5 minutes 1 hour before start of chemotherapy. Repeat dose of methylprednisolone at the initiation of chemotherapy and at the time of discharge. A chlorinated phenothiazine may also be used with the first dose of methylprednisolone for increased effect. **For severely emetogenic chemotherapy :** Administer 250mg IV over at least 5 minutes with appropriate doses of metoclopramide or a butyrophenone 1 hour before start of chemotherapy. Repeat dose of methylprednisolone at the initiation of chemotherapy and at the time of discharge.
Acute spinal cord injury	**Treatment should begin within 8 hours of injury :** For patients initiated on treatment within 3 hours of injury : Administer 30mg / kg as an IV bolus over a 15-minute period, followed by a 45 minute pause, and then a continuous IV infusion of 5.4mg / kg / h for 23 hours. For patients initiated on treatment within 3 to 8 hours of injury : Administer 30mg / kg as an IV bolus over a 15-minute period, followed by a 45-minute pause, and then a continuous IV infusion of 5.4mg / kg / h for 47 hours. There should be a separate intravenous site for the infusion pump.
As adjunctive therapy in other indications	Initial dose will vary from 10 to 500mg IV, depending on the clinical condition. Larger doses may be required for short-term management of severe, acute conditions. Initial doses up to 250mg should be administered IV over a period of at least 5 minutes, while larger doses should be administered over at least 30 minutes. Subsequent doses may be administered IV or IM at intervals dictated by the patient's response and clinical condition.

To avoid compatibility and stability problems, it is recommended that methylprednisolone sodium succinate be administered separately from other drugs whenever possible, as either IV push, through an IV medication chamber, or as an IV "piggy-back" solution or via an infusion pump.

Instruction for Use
Reconstitution : Under aseptic conditions add 7.8ml the bacteriostatic water for injection or sterile water for injection to the vial with sterile powder. The resulting solutions are physically and chemically stable for 48 hours at 25°C and at 2°C - 8°C. If desired, the medication may be administered in dilute solutions by admixing the reconstituted product with dextrose 5% in water, normal saline, dextrose 5% in 0.45% or 0.9% sodium chloride; the resulting solutions are physically and chemically stable for 24 hours at 25°C and 48 hours at 2°C - 8°C.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

CONTRAINDICATIONS:
Methylprednisolone sodium succinate is contraindicated :
- In patients who have systemic fungal infections
- In patients with known hypersensitivity to methylprednisolone or any component of the formulation
- For use by the intrathecal route of administration
- For use by the epidural route of administration.

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids.

PRECAUTIONS:
Immunosuppressant Effects / Increased Susceptibility to Infections :
Corticosteroids may increase susceptibility to infection, may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infections with any pathogen including viral, bacterial, fungal, protozoan or helminthic organisms, in any location in the body, may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents that affect cellular or humoral immunity, or neutrophil function. These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases. Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered to patients receiving immunosuppressive doses of corticosteroids; however, the response to such vaccines may be diminished. Indicated immunization procedures may be undertaken in patients receiving non-immunosuppressive doses of corticosteroids. The use of corticosteroids in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with appropriate anti-tuberculosis regimen. If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis. Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission. The role of corticosteroids in septic shock has been controversial, with early studies reporting both beneficial and detrimental effects. More recently, supplemental corticosteroids have been suggested to be beneficial in patients with established septic shock who exhibit adrenal insufficiency. However, their routine use in septic shock is not recommended. A systematic review of short-course, high-dose corticosteroids did not support their use. However, meta-analyses, and a review suggest that longer courses (5-11 days) of low-dose corticosteroids might reduce mortality, especially in patients with vasopressor-dependent septic shock.

Immune System Effects :
Allergic reactions may occur. Because rare instances of skin reactions and anaphylactic / anaphylactoid reactions have occurred in patients receiving corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug.

Endocrine Effects :
In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during and after the stressful situation is indicated. Pharmacologic doses of corticosteroids administered for prolonged periods may result in hypothalamic-pituitary-adrenal (HPA) suppression (secondary adrenocortical insufficiency). The degree and duration of adrenocortical insufficiency produced is variable among patients and depends on the dose, frequency, time of administration, and duration of glucocorticoid therapy. This effect may be minimized by use of alternate-day therapy. In addition, acute adrenal insufficiency leading to a fatal outcome may occur if glucocorticoids are withdrawn abruptly. Drug-induced secondary adrenocortical insufficiency may therefore be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. A steroid "withdrawal syndrome," seemingly unrelated to adrenocortical insufficiency, may also occur following abrupt discontinuance of glucocorticoids. This syndrome includes symptoms such as: anorexia, nausea, vomiting, lethargy, headache, fever, joint pain, desquamation, myalgia, weight loss, and/or hypotension. These effects are thought to be due to the sudden change in glucocorticoid concentration rather than to low corticosteroid levels. Because glucocorticoids can produce or aggravate Cushing's syndrome, glucocorticoids should be avoided in patients with Cushing's disease. There is an enhanced effect of corticosteroids on patients with hypothyroidism.

Metabolism and Nutrition :
Corticosteroids, including methylprednisolone, can increase blood glucose, worsen pre-existing diabetes, and predispose those on long-term corticosteroid therapy to diabetes mellitus.

Psychiatric Effects :
Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids. Potentially severe psychiatric adverse reactions may occur with systemic steroids. Symptoms typically emerge within a few days or weeks of starting treatment. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary. Psychological effects have been reported upon withdrawal of corticosteroids; the frequency is unknown. Patients/caregivers should be encouraged to seek medical attention if psychological symptoms develop in the patient, especially if depressed mood or suicidal ideation is suspected. Patients/caregivers should be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering / withdrawal of systemic steroids.

Nervous System Effects :
Corticosteroids should be used with caution in patients with seizure disorders. Corticosteroids should be used with caution in patients with myasthenia gravis. Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. Severe medical events have been reported in association with the intrathecal / epidural routes of administration. There have been reports of epidural lipomatosis in patients taking corticosteroids, typically with long-term use at high doses.

Ocular Effects :
Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation. Prolonged use of corticosteroids may produce posterior subcapsular cataracts and nuclear cataracts (particularly in children), exophthalmos, or increased intraocular pressure, which may result in glaucoma with possible damage to the optic nerves. Establishment of secondary fungal and viral infections of the eye may also be enhanced in patients receiving glucocorticoids. Corticosteroid therapy has been associated with central serous chorioretinopathy, which may lead to retinal detachment.

Cardiac Effects :
Adverse effects of glucocorticoids on the cardiovascular system, such as dyslipidemia and hypertension, may predispose treated patients with existing cardiovascular risk factors to additional cardiovascular effects, if high doses and prolonged courses are used. Accordingly, corticosteroids should be employed judiciously in such patients and attention should be paid to risk modification and additional cardiac monitoring if needed. Low dose and alternate day therapy may reduce the incidence of complications in corticosteroid therapy. There are reports of cardiac arrhythmias, and / or circulatory collapse, and/or cardiac arrest following the rapid administration of large intravenous doses of methylprednisolone sodium succinate (more than 0.5 g administered over a period of less than 10 minutes). Bradycardia has been reported during or after the administration of large doses of methylprednisolone sodium succinate, and may be unrelated to the speed or duration of infusion. Systemic corticosteroids should be used with caution, and only if strictly necessary, in cases of congestive heart failure.

Vascular Effects :
Thrombosis including venous thromboembolism has been reported to occur with corticosteroids. As a result corticosteroids should be used with caution in patients who have or may be predisposed to thromboembolic disorders. Steroids should be used with caution in patients with hypertension.

Gastrointestinal Effects :
High doses of corticosteroids may produce acute pancreatitis. There is no universal agreement on whether corticosteroids per se are responsible for peptic ulcers encountered during therapy; however, glucocorticoid therapy may mask the symptoms of peptic ulcer so that perforation or hemorrhage may occur without significant pain. Glucocorticoid therapy may mask peritonitis or other signs or symptoms associated with gastrointestinal disorders such as perforation, obstruction or pancreatitis. In combination with NSAIDs, the risk of developing gastrointestinal ulcers is increased. Corticosteroids should be used with caution in patients with non-specific ulcerative colitis if there is a probability of impending perforation, abscess, or other pyogenic infection, diverticulitis, fresh intestinal anastomoses, or active or latent peptic ulcer.

Hepatobiliary Effects :
Drug induced liver injury such as acute hepatitis can result from cyclical pulsed IV methylprednisolone (usually at doses of 1 g/day). The time to onset of acute hepatitis can be several weeks or longer. Resolution of the adverse event has been observed after treatment was discontinued.

Musculoskeletal Effects :
An acute myopathy has been reported with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g., myasthenia gravis), or in patients receiving concomitant therapy with anticholinergics, such as neuromuscular blocking drugs (e.g., pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevations of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years. Osteoporosis is a common but infrequently recognized adverse effect associated with a long-term use of large doses of glucocorticoid.

Renal and Urinary Disorders :
Caution is required in patients with systemic sclerosis because an increased incidence of scleroderma renal crisis has been observed with corticosteroids, including methylprednisolone. Corticosteroids should be used with caution in patients with renal insufficiency.

Scleroderma renal crisis :
Caution is required in patients with systemic sclerosis because of an increased incidence of (possibly fatal) scleroderma renal crisis with hypertension and decreased urinary output observed with a daily dose of 15 mg or more prednisolone.

Investigations :
Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Injury, Poisoning and Procedural Complications :
Systemic corticosteroids are not indicated for, and therefore, should not be used to treat, traumatic brain injury; a multicenter study revealed an increased mortality at 2 weeks and 6 months after injury in patients administered methylprednisolone sodium succinate compared to placebo. A causal association with methylprednisolone sodium succinate treatment has not been established.

Other :
Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk / benefit decision must be made in each individual case as to dose and duration of treatment as to whether daily or intermittent therapy should be used. The lowest possible dose of corticosteroid should be used to control the condition under treatment and when reduction in dosage is possible, the reduction should be gradual. Aspirin and nonsteroidal anti-inflammatory agents should be used cautiously in conjunction with corticosteroids. Pheochromocytoma crisis, which can be fatal, has been reported after administration of systemic corticosteroids. Corticosteroids should only be administered to patients with suspected or identified pheochromocytoma after an appropriate risk / benefit evaluation. In post marketing experience tumor lysis syndrome (TLS) has been reported in patients with malignancies, including hematological malignancies and solid tumors, following the use of systemic corticosteroids alone or in combination with other chemotherapeutic agents. Patients at high risk of TLS, such as patients with tumors that have a high proliferative rate, high tumor burden and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precautions should be taken.

Use in Children :
The recommended bacteriostatic water for injection contains the preservative benzyl alcohol has been associated with serious adverse events, including the "gasping syndrome", and death in pediatric patients. Although normal therapeutic doses of this product ordinarily deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the "gasping syndrome", the minimum amount of benzyl alcohol at which toxicity may occur is not known. The risk of benzyl alcohol toxicity depends on the quantity administered and the liver and kidneys' capacity to detoxify the chemical. Premature and low-birth weight infants may be more likely to develop toxicity. Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed. Growth may be suppressed in children receiving long-term, daily, divided-dose glucocorticoid therapy and use of such regimen should be restricted to the most urgent indications. Alternate-day glucocorticoid therapy usually avoids or minimizes this side effect. Infants and children on prolonged corticosteroid therapy are at special risk from raised intracranial pressure. High doses of corticosteroids may produce pancreatitis in children. Hypertrophic cardiomyopathy may develop after administration of methylprednisolone to prematurely born infants, therefore appropriate diagnostic evaluation and monitoring of cardiac function and structure should be performed.

FERTILITY, PREGNANCY AND LACTATION:

Fertility :
Corticosteroids have been shown to impair fertility in animal studies.

Pregnancy :
Animal studies have shown that corticosteroids, when administered to the mother at high doses, may cause fetal malformations. However, corticosteroids do not appear to cause congenital anomalies when given to pregnant women. Since adequate human reproductive studies have not been done with methylprednisolone sodium succinate, this medicinal product should be used during pregnancy only after a careful assessment of the benefit-risk ratio to the mother and fetus. Some corticosteroids readily cross the placenta. One retrospective study found an increased incidence of low-birth weights in infants born of mothers receiving corticosteroids. In humans, the risk of low birth weight appears to be dose related and may be minimized by administering lower corticosteroid doses. Infants born to mothers, who have received substantial doses of corticosteroids during pregnancy must be carefully observed and evaluated for signs of adrenal insufficiency, although neonatal adrenal insufficiency appears to be rare in infants who were exposed in utero to corticosteroids. There are no known effects of corticosteroids on labor and delivery. Cataracts have been observed in infants born to mothers treated with long-term corticosteroids during pregnancy. Benzyl alcohol can cross the placenta.

Lactation :
Corticosteroids are excreted in breast milk. Corticosteroids distributed into breast milk may suppress growth and interfere with endogenous glucocorticoid production in nursing infants. This medicinal product should be used during breast-feeding only after a careful assessment of the benefit-risk ratio to the mother and infant.

SIDE EFFECTS:

MedDRA System Organ Class	Frequency	Undesirable Effects
Infections and infestations	Not known	Opportunistic infection, Infection, Peritonitis#
Blood and lymphatic system disorders	Not known	Leukocytosis
Immune system disorders	Not known	Drug hypersensitivity, Anaphylactic reaction, Anaphylactoid reaction
Endocrine disorders	Not known	Cushingoid, Hypothalamic pituitary adrenal axis suppression, Steroid withdrawal syndrome
Metabolism and nutrition disorders	Not known	Metabolic acidosis, Sodium retention, Fluid retention, Alkalosis hypokalaemic, Dyslipidaemia, Glucose tolerance impaired, Increased insulin requirement (or oral hypoglycemic agents in diabetics), Lipomatosis, Increased appetite (which may result in Weight increased)
Psychiatric disorders	Not known	Affective disorder (including Depressed mood, Euphoric mood, Affect lability, Drug dependence, Suicidal ideation), Psychotic disorder (including Mania, Delusion, Hallucination, and Schizophrenia), Mental disorder, Personality change, Confusional state, Anxiety, Mood swings, Abnormal behaviour, Insomnia, Irritability
Nervous system disorders	Not known	Epidural lipomatosis, Intracranial pressure increased (with Papilloedema [Benign intracranial hypertension]), Seizure, Amnesia, Cognitive disorder, Dizziness, Headache
Eye disorders	Not known	Chorioretinopathy, Cataract, Glaucoma, Exophthalmos
Ear and labyrinth disorders	Not known	Vertigo
Cardiac disorders	Not known	Cardiac failure congestive (in susceptible patients), arrhythmia
Vascular disorders	Not known	Thrombosis, hypertension, hypotension, flushing
Respiratory, thoracic and mediastinal disorders	Not known	Pulmonary embolism, hiccups
Gastrointestinal disorders	Not known	Peptic ulcer (with possible Peptic ulcer perforation and Peptic ulcer haemorrhage), Intestinal perforation, Gastric haemorrhage, Pancreatitis, Oesophagitis ulcerative, Oesophagitis, Abdominal distension, Abdominal pain, Diarrhoea, Dyspepsia, Nausea
Skin and subcutaneous tissue disorders	Not known	Angioedema, Hirsutism, Petechiae, Ecchymosis, Skin atrophy, Erythema, Hyperhidrosis, Skin striae, Rash, Pruritus, Urticaria, Acne, Skin hypopigmentation
Musculoskeletal and connective tissue disorders	Not known	Muscular weakness, Myalgia, Myopathy, Muscle atrophy, Osteoporosis, Osteonecrosis, Pathological fracture, Neuropathic arthropathy, Arthralgia, Growth retardation
Reproductive system and breast disorders	Not known	Menstruation irregular
General disorders and administration site conditions	Not known	Impaired healing, Oedema peripheral, Fatigue, Malaise, Injection site reaction
Investigations	Not known	Intraocular pressure increased, Carbohydrate tolerance decreased, Blood potassium decreased, Urine calcium increased, Alanine aminotransferase increased, Aspartate aminotransferase increased; Blood alkaline phosphatase increased, Blood urea increased, Suppression of reactions to skin tests*
Injury, poisoning and procedural complications	Not known	Spinal compression fracture, Tendon rupture
Hepatobiliary disorders	Not known	Hepatitis†

The following adverse reactions have been reported with the following contraindicated routes of administration:
Intrathecal/Epidural: Arachnoiditis, functional gastrointestinal disorder/bladder dysfunction, headache, meningitis, paraparesis/paraplegia, seizure, sensory disturbance. The frequency of these adverse reactions is not known.

** Not a MedDRA PT*

† Hepatitis has been reported with IV administration.

 # Peritonitis may be the primary presenting sign or symptom of a gastrointestinal disorder such as perforation, obstruction or pancreatitis.

Effects on ability to drive and use machine :
The effect of corticosteroids on the ability to drive or use machinery has not been systematically evaluated. Undesirable effects, such as dizziness, vertigo, visual disturbances, and fatigue are possible after treatment with corticosteroids. If affected, patients should not drive or operate machinery.

DRUG INTERACTIONS:

Methylprednisolone is a cytochrome P450 enzyme (CYP) substrate and is mainly metabolized by the CYP3A4 enzyme. CYP3A4 is the dominant enzyme of the most abundant CYP subfamily in the liver of adult humans. It catalyzes 6β-hydroxylation of steroids, the essential Phase I metabolic step for both endogenous and synthetic corticosteroids. Many other compounds are also substrates of CYP3A4, some of which (as well as other drugs) have been shown to alter glucocorticoid metabolism by induction (upregulation) or inhibition of the CYP3A4 enzyme. CYP3A4 INHIBITORS - Drugs that inhibit CYP3A4 activity generally decrease hepatic clearance and increase the plasma concentration of CYP3A4 substrate medications, such as methylprednisolone. In the presence of a CYP3A4 inhibitor, the dose of methylprednisolone may need to be titrated to avoid steroid toxicity. CYP3A4 INDUCERS - Drugs that induce CYP3A4 activity generally increase hepatic clearance, resulting in decreased plasma concentration of medications that are substrates for CYP3A4. Coadministration may require an increase in methylprednisolone dosage to achieve the desired result. CYP3A4 SUBSTRATES - In the presence of another CYP3A4 substrate, the hepatic clearance of methylprednisolone may be affected, with corresponding dosage adjustments required. It is possible that adverse events associated with the use of either drug alone may be more likely to occur with coadministration. Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects. NON-CYP3A4-MEDIATED EFFECTS – Other interactions and effects that occur with methylprednisolone are described in Table below.

Drug Class or Type DRUG or SUBSTANCE	Interaction / Effect
Antibacterial - ISONIAZID	CYP3A4 INHIBITOR. In addition, there is a potential effect of methylprednisolone to increase the acetylation rate and clearance of isoniazid.
Antibiotic, Antitubercular - RIFAMPIN	CYP3A4 INDUCER
Anticoagulants (oral)	The effect of methylprednisolone on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulants when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effects.
Anticonvulsants - CARBAMAZEPINE	CYP3A4 INDUCER (and SUBSTRATE)
Anticonvulsants : - PHENOBARBITAL - PHENYTOIN	CYP3A4 INDUCERS
Anticholinergics : - NEUROMUSCULAR BLOCKERS	Corticosteroids may influence the effect of anticholinergics. 1) An acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking drugs. 2) Antagonism of the neuromuscular blocking effects of pancuronium and vecuronium has been reported in patients taking corticosteroids. This interaction may be expected with all competitive neuromuscular blockers.
Anticholinesterases	Steroids may reduce the effects of anticholinesterases in myasthenia gravis.
Antidiabetics	Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.
Antiemetic - APREPITANT - FOSAPREPITANT	CYP3A4 INHIBITORS (and SUBSTRATES)
Antifungal - ITRACONAZOLE - KETOCONAZOLE	CYP3A4 INHIBITORS (and SUBSTRATES)
Antivirals - HIV-PROTEASE INHIBITORS	CYP3A4 INHIBITORS (and SUBSTRATES) 1) Protease inhibitors, such as indinavir and ritonavir, may increase plasma concentrations of corticosteroids. 2) Corticosteroids may induce the metabolism of HIV-protease inhibitors resulting in reduced plasma concentrations.
Aromatase inhibitors - AMINOGLUTETHIMIDE	Aminoglutethimide-induced adrenal suppression may exacerbate endocrine changes caused by prolonged glucocorticoid treatment.
Calcium Channel Blocker - DILTIAZEM	CYP3A4 INHIBITOR (and SUBSTRATE)
Contraceptives (oral) - ETHINYLESTRADIOL / NORETHISTERONE	CYP3A4 INHIBITOR (and SUBSTRATE)
GRAPEFRUIT JUICE	CYP3A4 INHIBITOR
Immunosuppressant: - CYCLOSPORINE	CYP3A4 INHIBITOR (and SUBSTRATE). 1) Mutual inhibition of metabolism occurs with concurrent use of cyclosporine and methylprednisolone, which may increase the plasma concentrations of either or both drugs. Therefore, it is possible that adverse events associated with the use of either drug alone may be more likely to occur upon coadministration. 2) Convulsions have been reported with concurrent use of methylprednisolone and cyclosporine.
Immunosuppressant - CYCLOPHOSPHAMIDE - TACROLIMUS	CYP3A4 SUBSTRATES
Macrolide Antibacterial - CLARITHROMYCIN; - ERYTHROMYCIN	CYP3A4 INHIBITORS (and SUBSTRATES)
Macrolide Antibacterial - TROLEANDOMYCIN	CYP3A4 INHIBITOR
NSAIDs (nonsteroidal anti - inflammatory drugs) - high-dose ASPIRIN (acetylsalicylic acid)	1) There may be increased incidence of gastrointestinal bleeding and ulceration when corticosteroids are given with NSAIDs. 2) Methylprednisolone may increase the clearance of high-dose aspirin, which can lead to decreased salicylate serum levels. Discontinuation of methylprednisolone treatment can lead to raised salicylate serum levels, which could lead to an increased risk of salicylate toxicity.
Potassium depleting agents	When corticosteroids are administered concomitantly with potassium depleting agents (i.e., diuretics), patients should be observed closely for development of hypokalemia. There is also an increased risk of hypokalemia with concurrent use of corticosteroids with amphotericin B, xanthines, or beta2 agonists.

Incompatibilities :
To avoid compatibility and stability problems, it is recommended that methylprednisolone sodium succinate be administered separately from other compounds that are administered via the IV route of administration. Drugs that are physically incompatible in solution with methylprednisolone sodium succinate include, but are not limited to: allopurinol sodium, doxapram hydrochloride, tigecycline, diltiazem hydrochloride, calcium gluconate, vecuronium bromide, rocuronium bromide, cisatracurium besylate, glycopyrrolate, propofol.

OVERDOSAGE AND TREATMENT :

There is no clinical syndrome of acute overdosage with corticosteroids. Reports of acute toxicity and / or death following overdosage of corticosteroids are rare. In the event of overdosage, no specific antidote is available; treatment is supportive and symptomatic. Methylprednisolone is dialyzable.

STORAGE:

Unreconstituted product : Store below 30°C.
Reconstituted solution (with bacteriostatic water for injection or water for injection) : Store below 25°C or between 2°C - 8°C, use within 48 hours.
Admixture of reconstituted product : Store below 25°C, use within 24 hours, or between 2°C - 8°C, use within 48 hours.

From a microbiological point of view, freshly reconstituted solution is recommended.

KEEP OUT OF REACH OF CHILDREN
JAUHI DARI KANAK-KANAK

PACK QUANTITIES:

Available in one vial & 10 vials of sterile powder for injection per box.
Not all pack sizes may be marketed.

Further information can be obtained from pharmacist, physician or the manufacturer.

Product Registration Holder & Manufactured By :
Kotra Pharma (M) Sdn. Bhd. (90082-V)
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